

Tutorial

Mining and Model Understanding on Medical Data

Block 5: Learning from eHealth and mHealth Data

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INF

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eHealth and mHealth

Internet and smart technologies are already used to

- ▶ contribute to the diagnosis of a disease
- ▶ capture the symptoms of a disease for better/personalized therapy design
- ▶ deliver treatment

and ...

- ▶ foster research on diseases that are not well understood

In this block

we discuss

- ▶ treatment delivery via Internet
- ▶ symptom capturing and disease understanding with help of smart devices

and where “learning from data” fits into the picture.

taking (mostly)
the perspective of the
medical researcher

Agenda

- ▶ Using the Internet for Therapy
 - The case of iCBT

- ▶ The Promise of Smart Devices
 - to capture symptoms and to support treatments
 - From sensors to clinical targets: potential and challenges
 - Learning from mHealth data: the case of EMA

CBT

Quoting from [Cuijpers et al., 2008]

Cognitive-behavioral interventions are aimed at challenging negative automatic thoughts and dysfunctional underlying beliefs, and at changing behavioral patterns which are related to the problem being targeted in the therapy.

Cognitive-Behavioral Therapy (CBT)

is studied in hundreds of articles for a wide range of disorders and health problems, including

- ▶ depression
- ▶ anxiety disorders
- ▶ schizophrenia
- ▶ chronic pain
- ▶ headache
- ▶ cancer



CBT & iCBT – a decade₊₊ ago

“CBT is not only the most extensively researched form of psychotherapy, but also the most widely applied type of psychotherapy (Norcross et al. 2005), and certainly the most widely applied ‘evidence-based’ type of psychological therapy.” [Cuijpers et al., 2008]

In 2008, the potential of Internet for CBT had already been the subject of intensive study.

The beginnings:

2003: Special issue on internet-based CBT [Andersson and Carlbring, 2003]

2002: iCBT for distress associated with tinnitus [Andersson et al., 2002]

2001: Internet-based self-help treatment for panic disorder
[Carlbring et al., 2001]

2000: Internet-based self-help treatment for recurrent headache
[Ström et al., 2000] (accepted in **Nov. 1999**)

2000: Telepsychology via Internet for treatment of public speaking fear
[Botella et al., 2000] (work links to cognitive-behavior interventions)

The beginnings of Internet-based interventions (CBT)

2001: Quoting [Carlbring et al., 2001]
“Andersson and colleagues (Andersson, Strömgren, Ström, & Lyttkens, 2000) have adopted an approach more similar to previous minimal-therapist-contact self-help studies . . . , that is, using structured self-help manuals supported by a minimal amount of therapist support, often in the form of telephone contact. The main difference in Internet-based self-help treatment is that all material is provided via Web pages and that e-mail replaces telephone contact.”

The promise of Internet-based interventions (CBT)

2008:

Quoting [Cuijpers et al., 2008]

- ▶ save therapist time, reduce waiting-lists,
- ▶ allow patients to work at their own pace,
- ▶ abolish the need to schedule appointments with a therapist, save traveling time,
- ▶ reduce the stigma of going to a psychologist or therapist,
- ▶ facilitate help for the hard-of-hearing

- ▶ may be programmed to enhance patients' motivation by presenting a wide range of attractive audiovisual information with voices giving instructions in whichever gender, age, accent, language and perhaps game format the client prefers
- ▶ quickly and automatically report patient progress and self-ratings

Towards the promise of Internet-based CBT

Questions to be answered:

- ▶ How to design and deliver iCBT the way “the client prefers” ? KDD
- ▶ How to enhance the therapist-patient interaction, also for patients that are not very familiar with the Internet? KDD
- ▶ How to support data collection, processing and exploitation? KDD
- ▶ How to support the logistics of data collection, processing and exploitation?
- ▶ How to deliver iCBT?

and associated to them:

- △ How much therapist involvement is needed?
- △ For what disorders (and for which patients) **Does iCBT work?**

iCBT for depression

[Hallgren et al., 2015]

What do we know already?

“Several RCTs have assessed the effectiveness of iCBT on depression. ^{a b}”

“A recent review concludes that internet-based psychological treatments can be equally effective in treating mild to moderate depression as face-to-face CBT. ^c”

^{a12}: Moritz S, Schilling L, Hauschildt M, Schroder J, Treszl A. A randomized controlled trial of internet-based therapy in depression. *Behav Res Ther* 2012; 50: 513–21.

^{b13}: Wagner B, Horn AB, Maercker A. Internet-based versus face-to-face cognitive-behavioral intervention for depression: a randomized controlled non-inferiority trial. *J Affect Disord* 2014; 152–154: 113–21.

^{c14}: Andersson G, Cuijpers P, Carlbring P, Riper H, Hedman E. Guided Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: a systematic review and meta-analysis. *World Psychiatry* 2014; 13:288–95.

- ✓ iCBT does work
 - at least for mild to moderate depression
 - at least as well as face-to-face CBT (non-inferiority)

iCBT for depression

[Hallgren et al., 2015]

- ✓ iCBT does work
- at least for mild to moderate depression
 - at least as well as face-to-face CBT (non-inferiority)

Motivation

“Background” in [Hallgren et al., 2015]

Alternative treatments for depression that are

- ▶ non-stigmatizing
- ▶ accessible
- ▶ can be prescribed by general practitioners

Depression is recurrent.

Scientific aims of [Hallgren et al., 2015]

“To compare the effectiveness of three interventions for depression: physical exercise, internet-based cognitive-behavioural therapy (iCBT) and treatment as usual (TAU).

A secondary aim was to assess changes in self-rated work capacity.”

iCBT for depression

[Hallgren et al., 2015]

Method

946 patients diagnosed with mild or moderate depression, recruited through primary healthcare centres across Sweden, randomly assigned to one of three 12-week interventions and reassessed at 3 months.

Results

Patients in the iCBT group and in the physical exercise group reported larger improvements than patients in TAU.

Work capacity improved in all three groups, without significant differences among the groups.

Any ML in the analysis?

Descriptive statistics (percentages) to describe participant characteristics;
paired sample t-tests with Bonferroni correction;
analysis of covariance (ANCOVA);
multi-level model (patients & time: baseline to 3 months) (presumably linear)

Characterize the patients that did/didn't improve in each group and across groups?



iCBT for chronic tinnitus

Quoting from [Probst et al., 2019]

Motivation and Goals

iCBT is effective for chronic tinnitus, but several patients do not improve.



Analyse the role of baseline and progress variables for responders vs non-responders.

Approach

Definition of “non-responder”: less than 7 points of improvement in the THI ^a score (75 responders, 21+7 non-responders);

Re-analysis of the data from two RCTs on iCBT for chronic tinnitus;

Investigation of associations between non-response and the values of

- baseline variables (age, gender, and questionnaire scores)
- the progress of the patients according to the THI questionnaire
- the 12 items of the WAI-SR questionnaire ^b, recorded at 1st, 2nd and 5th week of treatment
- other process variables (#logins, #messages sent from therapists to patients)

^aTinnitus Handicap Inventory questionnaire

^b“Working Alliance Inventory-Short Revised”



iCBT for chronic tinnitus

Quoting from [Probst et al., 2019]

Results

Non-responders had a less favorable THI-score change already at mid-treatment ($p < .05$).

Non-responders showed more severe sleep disturbances, logged in less in the iCBT platform, and received fewer messages from the therapists than responders, but these differences were mostly not significant after correcting for multiple testing.

Any ML in the analysis?

Chi-squared tests to compare non-responders and responders in gender;
Analysis of covariance in numerical baseline variables, # logins, # messages;

Multi-level models for discontinuous change with level-1 referring to

(a) the course of THI for responders vs non-responders and

(b) the course of WAI-SR for responders vs non-responders, during the iCBT therapy.

iCBT for paediatric OCD - using ML

[Lenhard et al., 2018]

Background and goals

“No consistent predictors of treatment outcome in paediatric Obsessive-Compulsive Disorder. One reason for this might be the use of suboptimal statistical methodology.”

⇒ Compare ML methods to conventional regression on OCD patients that have received iCBT, for the task of characterizing responders vs non-responders.

Data

67 adolescents exposed to immediate iCBT vs 12-weeks delayed iCBT (6 dropouts).
41% (of the 61) characterized as responders.

Analysis on 46 variables – demographics and questionnaire scores; single questionnaire items skipped to facilitate the classical regression.

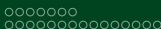
ML methods

- Linear model with selection of the best subset of predictor variables
- L1 Elastic Net (Lasso)
- RF
- SVM with radial kernel

Results

ML methods identified predictor variables.

Conventional regression did not.



ML in the analyses of iCBT-related studies

Examples:

- ▶ [Månsson et al., 2015]: SVMs are trained on brain fMRI and on structured data to predict the long-term outcome (one year later) of iCBT for social anxiety disorder
- ▶ [Lenhard et al., 2018]: ML methods are trained to predict the outcome of iCBT for paediatric obsessive-compulsive disorder (OCD)
- ▶ [Wallert et al., 2018]: RFs are trained to predict adherence to iCBT (3 or more homework assignments ($\geq 21\%$ of total treatment) for patients in rehabilitation after myocardial infarction

as well as studies analyzing unstructured data (eg brain images) in the context of classical CBT.

Summarizing on ML usage

- ▶ ML to exploit images, brain signals, fMRI and other unstructured data
- ▶ ML to characterize patients (eg responders vs non-responders)

mostly for simple learning tasks

The promise of smart devices

- ▶ From sensor data to clinical targets
- ▶ A case example: Learning from Ecological Momentary Assessments

Smartphone adoption by seniors

[Berenguer et al., 2016]

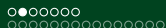
- ▶ Smartphone “penetration” among the 55+ users in Europe, USA, Asia: upward tendencies for the most age strata
- ▶ Large differences in usage habits and preferred features between young users and 55+ users
- ▶ Searches for health conditions are less popular among the seniors

but these numbers evolve fast.

Potential of the mHealth technologies

[Kumar et al., 2013]

Figure 1 from [Kumar et al., 2013] removed



Moving across the arrow of the mHealth potential

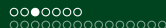
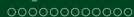
[Kumar et al., 2013]: mHealth for

Measurement → Diagnostic → Treatment/prevention → Global



Conversion of the

“raw sensor data into meaningful information related to behaviors, thoughts, emotions . . . and clinical states and disorders.” [Mohr et al., 2017]



Converting sensor data into information [Mohr et al., 2017]

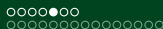
The “sensemaking” approach of [Mohr et al., 2017]:

- ★ Clinical state
- ↑ “Behavioral marker: behaviors, thoughts, feelings, traits, or states . . .”
- ↑ “[Low level] feature: a measureable property of a phenomenon, which is proximal to, and constructed from, sensor data”
- ↑ Raw sensor data

From raw data to clinical states

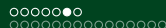
[Mohr et al., 2017]

Figure 1 from [Mohr et al., 2017] removed



Example from the framework of [Mohr et al., 2017], using the survey of [Aledavood et al., 2019] on sleep tracking:

	Fig.1 [Mohr et al., 2017]	Survey by [Aledavood et al., 2019]
<i>Clinical state</i>	Depression	
<i>Behavioral marker</i>	Sleep disruption	Emens J, Lewy A, Kinzie JM, Arntz D, Rough J. <i>Circadian misalignment in major depressive disorder</i> . <i>Psychiatry research</i> . 2009;168(3):259-61.
<i>Features</i>	Bedtime/Waketime Phone usage	Abdullah S, Matthews M, Murnane EL, Gay G, Choudhury T. <i>Towards circadian computing: early to bed and early to rise makes some of us unhealthy and sleep deprived</i> . In Proc. of the 2014 ACM Int. Joint Conf. on Pervasive and Ubiquitous Computing 2014;673-684. Murnane EL, Abdullah S, Matthews M, Choudhury T, Gay G. <i>Social (media) jet lag: How usage of social technology can modulate and reflect circadian rhythms</i> . In Proc. of the 2015 ACM Int. Joint Conf. on Pervasive and Ubiquitous Computing 2015;843-854.
<i>Sensors</i>	Phone screen, phone apps, ambient light, movement	



Challenges for smartphone apps in mHealth

<i>Challenge</i> [Torous et al., 2019]	<i>Recommendations</i> [Torous et al., 2019]	<i>ML Challenge</i>
Data safety and privacy	standards and transparent policies for data storage, use and sharing, including sharing with external partners; opt-out of sharing; policies in simple language; technical security reviews and data audits	privacy-preserving data access and learning; methods that forget users who opt out; learning on little data
App effectiveness	RCT	methods for patient recruitment; analysis of clinical studies; causal inference
User experience / adherence	user-centered design and evaluation; best practices	methods that capture (non-) adherence; methods that work with little data
Data integration	interoperability with EHR; process documentation; adherence to interoperability standards	methods that learn from clinical and mHealth data; methods that keep the medical expert in the loop

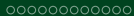
Moving across the arrow of the mHealth potential

[Kumar et al., 2013]: mHealth for

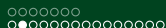
Measurement → Diagnostic → Treatment/prevention → Global

EMA: From Measurement onwards

<i>Stage</i>	<i>Clinical target</i>
Measurement: EMA	Tinnitus and co-morbidities
Diagnostic: sensor-sampling for diagnostics	time-of-day effects of tinnitus
Treatment/prevention: Chronic disease management	assessment prediction
Global: Disease surveillance	...



Ecological Momentary Assessments



EMA as an instrument

“Experience sampling”

[Csikszentmihalyi and Larson, 2014]

Quoting from https://link.springer.com/chapter/10.1007/978-94-017-9088-8_3:

... The Experience-Sampling Method (ESM) is an attempt to provide a valid instrument to describe variations in self-reports of mental processes. It can be used to obtain empirical data on the following types of variables: (a) frequency and patterning of daily activity, social interaction, and changes in location; (b) frequency, intensity, and patterning of psychological states, i.e., emotional, cognitive, and conative dimensions of experience; (c) frequency and patterning of thoughts, including quality and intensity of thought disturbance. The article reviews practical and methodological issues of the ESM and presents evidence for its short-and long-term reliability when used as an instrument for assessing the variables outlined above.

(Copyright 1987, Wolters Kluwer Health)



EMA as an instrument

“Ecological Momentary Assessment”

[Stone and Shiffman, 1994]

Quoting from <https://psycnet.apa.org/record/1995-10701-001>:

Discusses ecological momentary assessments (EMAs), recently developed approaches for assessing behavioral and cognitive processes in their natural settings. Four qualities define EMA methods: 1) phenomena are assessed as they occur, 2) assessments are dependent upon careful timing, 3) assessments usually involve a substantial number of repeated observations, and 4) assessments are usually made in the environment that the S typically inhabits. Phenomena for which EMAs are relevant are reviewed, particularly rapidly fluctuating processes such as affect, pain perception, and coping efforts...

(PsycINFO Database Record (c) 2019 APA, all rights reserved)



EMA as an instrument

“Experience sampling” [Csikszentmihalyi and Larson, 2014]

“Ecological Momentary Assessment” [Stone and Shiffman, 1994]

“Ambulatory assessment” [Fahrenberg et al., 2007]

Quoting from <https://psycnet.apa.org/record/2007-18155-002>:

Ambulatory assessment refers to the use of computer-assisted methodology for self-reports, behavior records, or physiological measurements, while the participant undergoes normal daily activities. . . .

EMA in an example

Quoting from [Probst et al., 2017]

Users of the TrackYourTinnitus app “were asked to rate at each notification:”

Three subjective ratings on a visual analog scale [VAS]:

<i>Variable</i>	<i>Range</i>
Current tinnitus loudness	0 (moment without sound) ... 1
Current tinnitus distress	0 (moment without distress) ... 1
Current stress level	0 ... 1

“Moreover, the timestamps of the assessments were used to explore the time-of-day-dependence of tinnitus.”

Why monitor tinnitus day-by-day with EMA?

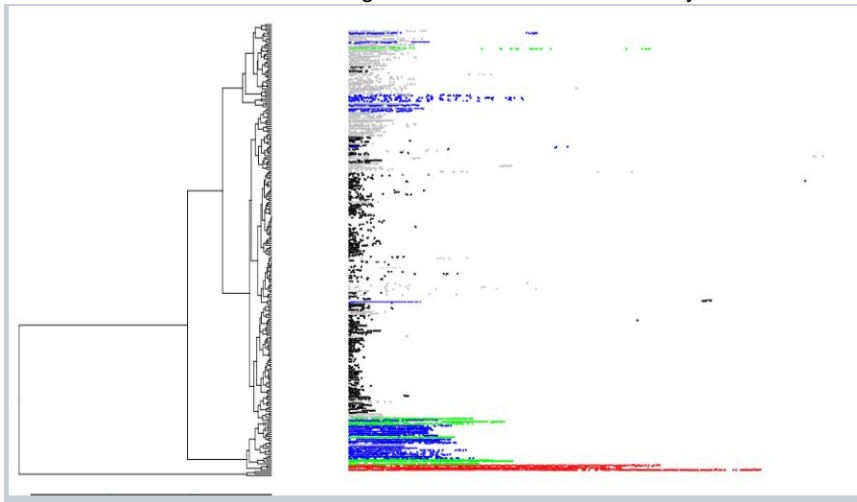
Patient response to treatment varies a lot. Two possible explanations:

- tinnitus varies across patients
- for a given patient, tinnitus varies with the time of day

EMA as series of timestamps

[Unnikrishnan, 2017]

Time series of TYT users – left aligned and clustered on similarity



EMA for Learning

EMA constitute one multi-dimensional time series per patient.

1. Analyzing EMA to understand tinnitus symptoms [Probst et al., 2017]
2. Analyzing EMA to predict tinnitus symptoms for different patient phenotypes [Unnikrishnan et al., 2019]



Understand tinnitus symptoms with EMA from the TrackYourTinnitus app

[Probst et al., 2017, Pryss et al., 2017]

Patient registration data

Three questionnaires:

- ▶ Mini-TQ-12 on tinnitus-related psychological problems
- ▶ TSCHQ (37) on tinnitus sample case history
- ▶ Worst Symptom Questionnaire (9)

EMA time series

7 questions (up to 12 times a day) on:

- ▶ tinnitus loudness
- ▶ distress through tinnitus
- ▶ valence and arousal
- ▶ Ambient sounds captured during each EMA recording

Data for learning

- ▶ *Static*: 58 variables – numerical (VAS), categorical, binary
- ▶ *Time series*: 7 variables – one timestamp per variable recording, up to 7-12 recordings per day per patient

Data preparation

[Probst et al., 2017]

Specifying day and night intervals

- night: 12am–4am
- esarly morning: 4am–8am
- early evening: 4pm–8pm
- afternoon: 12pm–4pm
- late morning: 8am–12pm
- late evening: 8pm–12am

25,863 assessments

Data cleaning

Removal of:

- ▶ assessments with missing values in one of the target vars → 25,092
- ▶ days with less than three assessments → 17,209

Retained: 17,209 assessments from 350 participants

- 253m/94f; average age: 45.4 (over 333, SD=12.1)
- median time since tinnitus onset: 5.4Y (from 0 to 61.8Y)
- median days per participant: 11 (from 1 to 415)
- median number of assessments per day: 4 (from 3 to 18)

Understanding tinnitus symptoms

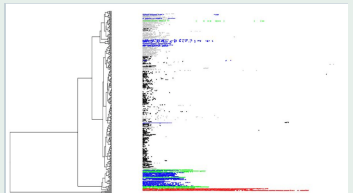
[Probst et al., 2017]

Selection of findings:

- ▶ “tinnitus was significantly louder in the late evening compared to the afternoon and early evening.”
- ▶ “stress-level increased from morning to afternoon, decreased from afternoon to evening, and did not differ compared to the night”
- ▶ “Tinnitus was louder and more distressing when the level of stress was higher at a specific time-of- day compared to other times-of-day, when it was higher during a whole day compared to other days, and when it was higher during the whole assessment period for a given participant (compared to other participants).”
- ▶ “the effects of time-of-day on tinnitus loudness and tinnitus distress were still significant (i.e., after controlling for the effects of stress).”

EMA as time series with gaps

RECALL [Unnikrishnan, 2017]



Removed EMA in [Probst et al., 2017]

MCAR or MNAR?

- 0.03% EMA with missing values in one of the three target variables
- 31.41% EMA in days with less than three assessments
- EMA for days with ≥ 3 assessments: median 4, max 18

EMA on TYT for prediction of tinnitus symptoms

[Unnikrishnan et al., 2019]

Modeling the prediction problem

Given is a set of participants, for the EMA of whom we have the distress values - but only for the first m EMA. For each patient x and EMA $o_{x,j}$ with $j > m$, predict the distress value of $o_{x,j}$.

Data cleaning

Removal of:

- ▶ participants with less than 5 EMA → 516 participants

Histogram: #days per participant

Figure removed



EMA on TYT for prediction of tinnitus symptoms

[Unnikrishnan et al., 2019]

3. kNN-based predictors in D_{EMA}

- ▶ Predictor 1 (model augmentation):
for each y in the neighbourhood of x (including x), learn a linear regression model m_y ;
average the parameters $m_{y,slope}$ and $m_{y,intercept}$ into a final model m_x .
- ▶ Predictor 2 (data augmentation):
place all EMA of x and of its neighbours into a pool;
learn a linear regression model for m_x over the pool

2. Exploiting the EMA dataset D_{EMA} and the registration data D_R for learning

- ▶ The kNN neighbourhood of each participant x is built on D_R
- ▶ Time series of participants are aligned across the time axis – no gaps are filled in D_{EMA}

EMA and phenotypes for prediction of tinnitus symptoms

[Unnikrishnan et al., 2019]

1. Combining tinnitus loudness and distress levels on D_R

Three clusters on loudness and two clusters on distress levels:

<i>Tinnitus Loudness</i>	<i>Tinnitus Distress</i>					
	#P	<i>Low TD</i>		#P	<i>High TD</i>	
Avg TD		Avg TL	Avg TD		Avg TL	
<i>Low TL</i>	81	7.4	Avg TL: 28.1	52	15.7	Avg TL: 26.8
<i>Mod TL</i>	83	8.1	Avg TL: 53.0	168	17.0	Avg TL: 54.4
<i>High TL</i>	35	9.2	Avg TL: 77.1	97	18.3	Avg TL: 82.2

Prediction for the six phenotypes

[Unnikrishnan et al., 2019]

Figure 17 removed

Takeaway messages from this Block

- ▶ Medical researchers and healthcare professionals increasingly use e- and m-technologies for diagnostics and treatment.
There is acceptance among patients, some times also eagerness.
- ▶ The technologies for raw data processing are mature.
The technologies for going all the way to the clinical targets are less so.
- ▶ Challenges ahead:
 - ★ Very few data per patient
 - ★ Gaps, data that are not necessarily missing at random
- ▶ Challenges inherent:
 - ★ Patient empowerment: how to increase and sustain adherence?
 - ★ Practitioner involvement:
 - explaining to the practitioner
 - understanding the effort required from the practitioner
 - incorporating practitioner - patient interaction into the service

THANK YOU !



VISIT THE KMD LAB:

The epi-mining team:

- ▶ Tommy Hielscher (constraint-based learning)
- ▶ Uli Niemann
(learners & workflows, visual analytics)

The mHealth-mining team:

- ▶ Miro Schleicher (adherence)
- ▶ Vishnu Unnikrishnan
(stream learning, similarity-based predictors)
- ▶ Christian Beyer
(stream learning, active learners)



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